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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

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22

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/713,136	TUCK ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this c mmunication appears on the c ver sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7,8 and 11-107* is/are pending in the application.

4a) Of the above claim(s) *11-49,52-59,62,64-70,73,76-82,85 and 87-89* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7,8,50,51,60,61,63,71,72,74,75,83,84,86 and 90-107* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/14/03 has been entered.

2. Claims 1-3, 7-8, and 11-107 are pending.

3. Claims 11-49, 52-59, 62, 64-70, 73, 76-82, 85, and 87-89 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-3, 7-8, 50-51, 60-61, 63, 71-72, 74-75, 83-84, 86, and 90-107 that read on species "Amb a1" as the specific antigen and "AACGTTCG" as a specific ISS are being acted upon in this Office Action.

5. The drawings, filed 11/14/00, stand not approved. Please see enclosed PTO 948, Notice of Draftsperson's Patent Drawing Review mailed 11/5/01. Appropriate action is required.

6. Claim 50 is objected to because said claim depends from non-elected claim 45.

7. Claim 60 is objected to because said claim depends from non-elected claim 55.

8. Claim 71 is objected to because said claim depends from non-elected claim 66.

9. Claim 83 is objected to because said claim depends from non-elected claim 78.

10. Claim 72 is objected to because "is comprises". It should have been either "is" or "comprises". If the sequence is intended to be open-ended, the Office prefers "comprises". If the sequence is intended to be close, the Office prefers "consisting of".

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-3, 7-8, 50-51, 60-61, 63, 71-72, 74-75, 83-84, 86, and 90-107 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a population of conjugate molecules said molecules comprising a ragweed pollen allergen such as Amb a1 and an immunostimulatory sequence (ISS) wherein said immunostimulatory sequence *consisting* of the sequence selected from the group consisting of SEQ ID NO: 1-8, and wherein the extent of conjugation in the population is such that the ratio of (i) concentration of ISS-antigen conjugate to (ii) concentration of antigen required for 50% inhibition of antigen-specific antibody to antigen is about 3.5 to about 6.0; (2) A population of conjugate molecules said molecules comprising a ragweed pollen allergen such as Amb a1 and an immunostimulatory sequence (ISS) wherein said immunostimulatory sequence *consisting* of the sequence selected from the group consisting of SEQ ID NO: 1-8, and wherein the extent of conjugation in the population provides a 40% histamine release from basophiles of an allergen-sensitized individual is greater than about 500, said ratio is calculated as the ratio of (i) concentration of ISS-allergen conjugate to (ii) concentration of antigen required for 40% histamine release from basophiles from an allergen sensitized individual; (3) A population of conjugate molecules, said conjugate molecules comprising a ragweed pollen allergen such as Amb a1 and a polynucleotide *consisting* of an immunostimulatory sequence (ISS) wherein said immunostimulatory sequence consisting of the sequence selected from the group consisting of SEQ ID NO: 1-8, and wherein the extent of conjugation in the population provides an average of at least 5.5 ISS-containing polynucleotides per antigen molecule; (4) A composition comprising the population of conjugate molecules, said conjugate molecules comprising a ragweed pollen allergen and a polynucleotide *consisting* of an immunostimulatory sequence (ISS) wherein said immunostimulatory sequence *consisting* of the sequence selected from the group consisting of SEQ ID NO: 1-8, and wherein the extent of conjugation in the population provides an average of at least 5.5 ISS-containing polynucleotides per antigen molecule in a pharmaceutically acceptable excipient; (5) A population of conjugate molecules said molecules comprising a ragweed pollen allergen such as Amb a1 and an immunostimulatory sequence (ISS) wherein said immunostimulatory sequence consisting of the sequence such as the ones recited in claims 79, 81, 82, 84 and 85, and wherein the extent of

conjugation in the population provides an average of ratio of (i) average mass of ISS-containing polynucleotide to (ii) average mass of antigen of at least 1.1; (6) A composition comprising the population of conjugate molecules said molecules comprising a ragweed pollen allergen such as Amb a1 and an immunostimulatory sequence (ISS) wherein said immunostimulatory sequence consisting of the sequence selected from the group consisting of SEQ ID NO: 1-8, and wherein the extent of conjugation in the population provides an average of ratio of (i) average mass of ISS-containing polynucleotide to (ii) average mass of antigen of at least 1.1 in a pharmaceutically acceptable excipient for treating allergy, **does not** reasonably provide enablement for

(1) *any* population of conjugate molecules, said conjugate molecule comprising *any* "antigen" such as *any* polypeptide, *any* allergen, *any* pollen allergen, *any* ragweed allergen, and *any* "polynucleotide" comprising *any* immunostimulatory sequence (ISS), wherein the polynucleotide is "greater than 6 and less than about 200 nucleotides in length" and wherein the extent of conjugation in the population is such that the ratio of (i) concentration of ISS-antigen conjugate required for 50% inhibition of binding of antigen-specific antibody to antigen to (ii) concentration of antigen required for 50% inhibition of binding of antigen-specific antibody to antigen is about 3.5 to about 6.0;

(2) *any* population of conjugate molecules, said conjugate molecules comprising *any* antigen such as *any* polypeptide, *any* allergen, any pollen allergen, *any* ragweed allergen and *any* polynucleotide comprising any immunostimulatory sequence (ISS), wherein the polynucleotide is "greater than 6 and less than about 200 nucleotides in length" and wherein the allergen is *any* allergen and wherein the extent of conjugation in the population provides a 40% histamine-release ratio of greater than about 500, said ratio calculated as the ratio of (i) concentration of ISS-antigen conjugate required for about 40% histamine release from basophiles from an antigen-sensitized individual to (ii) concentration of antigen required for about 40% histamine release from basophiles from an antigen-sensitized individual;

(3) the population of conjugate molecules, said conjugate molecules comprising *any* antigen and *any* polynucleotide comprising any immunostimulatory sequence (ISS), wherein the polynucleotide is "greater than 6 and less than about 200 nucleotides in length" and wherein the allergen is wherein the allergen is Amb a 1 and wherein the extent of conjugation in the population provides a 40% histamine-release ratio of greater than about 500, said ratio calculated as the ratio of (i) concentration of ISS-antigen conjugate required for about 40% histamine release

from basophiles from an antigen-sensitized individual to (ii) concentration of antigen required for about 40% histamine release from basophiles from an antigen-sensitized individual;

(4) *Any* composition comprising the population of conjugate molecules, said conjugate molecule comprising *any* antigen, *any* polypeptide, *any* allergen, *any* pollen allergen, *any* ragweed allergen, and *any* "polynucleotide" comprising *any* immunostimulatory sequence (ISS), wherein the extent of conjugation in the population is such that the ratio of (i) concentration of ISS-antigen conjugate required for 50% inhibition of binding of antigen-specific antibody to antigen to (ii) concentration of antigen required for 50% inhibition of binding of antigen-specific antibody to antigen is about 3.5 to about 6.0 in a pharmaceutically acceptable excipient;

(5) *Any* composition comprising the population of conjugate molecules, said conjugate molecule comprising *any* "antigen" such as *any* allergen, *any* pollen allergen, *any* ragweed allergen, and *any* "polynucleotide" comprising *any* immunostimulatory sequence (ISS), wherein the polynucleotide is "greater than 6 and less than about 200 nucleotides in length" and wherein the extent of conjugation in the population provides a 40% histamine-release ratio of greater than about 500, said ratio calculated as the ratio of (i) concentration of ISS-antigen conjugate required for about 40% histamine release from basophiles from an antigen-sensitized individual to (ii) concentration of antigen required for about 40% histamine release from basophiles from an antigen-sensitized individual in a pharmaceutically acceptable excipient;

(6) *Any* composition comprising the population of conjugate molecules, said conjugate molecules comprising *any* antigen such as *any* polypeptide, *any* allergen, any pollen allergen, *any* ragweed allergen and *any* polynucleotide comprising any immunostimulatory sequence (ISS), wherein the polynucleotide is "greater than 6 and less than about 200 nucleotides in length and wherein the allergen is *any* allergen and wherein the extent of conjugation in the population provides a 40% histamine-release ratio of greater than about 500, said ratio calculated as the ratio of (i) concentration of ISS-antigen conjugate required for about 40% histamine release from basophiles from an antigen-sensitized individual to (ii) concentration of antigen required for about 40% histamine release from basophiles from an antigen-sensitized individual in a pharmaceutically acceptable excipient;

(7) *any* population of conjugated molecules mentioned above wherein said immunostimulatory sequence "comprises" the sequence 5'-purine, purine, C,G, pyrimidine, pyrimidine, C, G-3';

(8) *any* population of said conjugated molecules *any* population of said conjugated molecules wherein said immunostimulatory sequence "comprises" the sequence 5'-purine, purine, C,G, pyrimidine, pyrimidine, C, G-3'wherein said immunostimulatory sequence "comprises" the sequence as set forth in claims 51 and 61;

(9) *any* population of conjugate molecules, said conjugate molecules comprising any antigen, and *any* polynucleotide comprising any immunostimulatory sequence (ISS), wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length and wherein the extent of conjugation in the population provides an average of at least 5.5 ISS containing polynucleotides per antigen molecule,

(10) *any* population of conjugate molecules, said conjugate molecules comprising any antigen such as any polypeptide, any allergen, any pollen allergen, any ragweed allergen, and *any* polynucleotide comprising any immunostimulatory sequence (ISS), wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length, wherein the extent of conjugation in the population in the population provides an average of (i) average mass of ISS-containing polynucleotide to (ii) average mass of antigen of at least 1.1 and

(11) The populations mentioned above wherein said immunostimulatory sequence "**comprises**" a sequence "comprises" *any* 5'-purine, purine, C,G, pyrimidine, pyrimidine, C, G-3', or *any* sequence "comprises" AACGTTCG as recited in claims 50-51, 60-61, 71-72, and 73-84 for treating *any* condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only eight specific immunostimulatory sequences (ISS) such as SEQ ID NO: 1-8 conjugated to ragweed allergen Amb a1 (See page 72). The conjugate was prepared by incubation of a mixture of ISS at various molar concentrations such as 4, 7 or 17

molar to 1 molar concentration of Amb a1. The antibody response and histamine release from various conjugates such as AIC-L (4:1), AIC-M (7:1) and AIC-H (17-1) are measured. The AIC-H (17-1) conjugate shift the Th2 to Th1 immune response as determined by IFNγ, IL-5 levels and histamine release (page 80-82). The specification discloses the term "antigen" means any substance such as peptides, proteins, glycoproteins, polysaccharides, complex carbohydrates, sugars, gangliosides lipids, and phospholipids; portions thereof and combination thereof (page 16, liens 20-22). The specification discloses that the term "allergen" means antigen, or antigenic portion thereof of any molecule, usually a protein (see 18, lines 12-14).

The specification does not teach how to make a population of conjugate comprising *any* antigen, *any* allergen, any polypeptide, and any immunostimulatory sequence "comprising" any sequence such as the ones mentioned above, much less using any undisclosed conjugate for treating *any* condition. The term "antigen", "polypeptide" and "allergen" without the specific amino acid sequence or SEQ ID NO has no structure much less function. Further, the term polynucleotide comprising an immunostimulatory sequence (ISS) wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length without the specific nucleotides has no structure, let alone it is immunostimulatory activity.

Stryer *et al*, of record, teach a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed relevant pages).

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Van Uden *et al* (PTO 1449) teach even after intensive attempts to precisely define the DNA sequence structure required for immune stimulation, this most fundamental aspect of ISS is only partially understood (See page 903, in particular).

Segal *et al* teach that immunostimulatory sequences such as CpG oligonucleotides are potent adjuvant for triggering autoimmune disease in predisposed susceptible individual (See abstract, in particular).

Yamada *et al* teach that the sequence and length of a DNA strand determine its activity and depending on how these polynucleotide's secondary/tertiary structure are fold, activity may be gained or lost (See page 5593, column 2, second full paragraph, in particular). Given the

indefinite number of antigen conjugated to indefinite number of undisclosed ISS, there is insufficient working examples demonstrating that any conjugate molecules mentioned above is immunostimulatory, let alone useful for treating any disease.

Without the specific amino acid sequence for the antigen and the specific nucleotide sequence even thought said polynucleotide must be greater than 6 and less than about 200 nucleotide in length, it is unpredictable which undisclosed population of conjugate molecules comprising any undisclosed antigen and undisclosed polynucleotide is immunostimulatory, and effective for treating any disease. Since the antigen and polynucleotide are not enabled, it follows that any conjugate molecule comprising said undisclosed antigen and said undisclosed ISS are not enabled. It also follows that any composition comprising said undisclosed population of conjugate are not enabled.

As to claims 50, 51, 60, 61, 71, 72, 83, and 84, the term "comprising" is open-ended. It expands the ISS in the conjugate to include additional nucleotides at either or both ends of the undisclosed ISS so long the ISS is greater than 6 and less than about 200 nucleotide in length. However, without the specific nucleotide sequence, it is unpredictable which undisclosed ISS in the conjugate would have immunostimulatory activity since Yamada *et al* teach that the sequence and length of a DNA strand determine its activity and depending on how these polynucleotide's secondary/tertiary structure are fold, activity may be gained or lost (See page 5593, column 2, second full paragraph, in particular), in addition to the potential of inducing autoimmune disease in susceptible individual as taught by Segal *et al* (See abstract, Figure 3, in particular).

For these reasons, it would require undue experimentation even for one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 4/14/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) amended claims 1, 2, 60, 63 and 75 have been amended. (2) Means of assessing the structural and functional characteristics of a population of conjugate molecules are provided on page 28-36. (3) The term "antigen" means any substance that is recognized and bound specifically by any antibody or by a T cell antigen receptor" is defined in the specification on page 16, lines 19-20. (4) It is merely routine experimentation since the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceeded.

However, the claims still encompass any antigen, and any nucleotide polynucleotide comprising any immunostimulatory sequence (ISS) wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length in the claimed conjugate molecule. The specification does not teach how to make much less how to use any population of conjugate comprising *any* antigen, *any* allergen, any polypeptide, and any immunostimulatory sequence "comprising" any sequence such as the ones mentioned above, much less using any undisclosed conjugate for treating *any* condition. The term "antigen", "polypeptide" and "allergen" without the specific amino acid sequence or SEQ ID NO has no structure much less function. Further, the term polynucleotide comprising an immunostimulatory sequence (ISS) wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length without the specific nucleotides has no structure, let alone it is immunostimulatory activity. The term "antigen", "polypeptide" and "allergen" without the specific amino acid sequence or SEQ ID NO has no structure much less function. Further, the term polynucleotide comprising an immunostimulatory sequence (ISS) wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length without the specific nucleotides has no structure, let alone it is immunostimulatory activity. Without the specific amino acid sequence for the antigen and the specific polynucleotide that is greater than 6 and less than about 200 nucleotides in length has immunostimulatory activity, it is unpredictable which undisclosed population of conjugate molecules comprising any undisclosed antigen and undisclosed polynucleotide is immunostimulatory, and effective for treating any disease. Stryer *et al*, of record, teach a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed relevant pages). Segal *et al* teach that immunostimulatory sequences such as CpG oligonucleotides are potent adjuvant for triggering autoimmune disease in predisposed susceptible individual (See abstract, in particular).

Yamada *et al* teach that the sequence and length of a DNA strand determine its activity and depending on how these polynucleotide's secondary/tertiary structure are fold, activity may be gained or lost (See page 5593, column 2, second full paragraph, in particular). The working examples in the specification as filed indicate that none of the ISS in the population of conjugate is less than about 200 nucleotides in length. Given the indefinite number of antigen conjugated to indefinite number of undisclosed ISS, there is insufficient working examples demonstrating that any conjugate molecules mentioned above is immunostimulatory, let alone useful for treating any disease.

As to claims 50, 51, 60, 61, 71, 72, 83, and 84, the term "comprising" is open-ended. It expands the ISS in the conjugate to include additional nucleotides at either or both ends of the undisclosed ISS so long the ISS is greater than 6 and less than about 200 nucleotide in length. Further, the ISS without the specific nucleotide sequence has no structure. Without the specific nucleotide sequence, it is unpredictable which undisclosed ISS in the conjugate would have immunostimulatory activity since Yamada *et al* teach that the sequence and length of a DNA strand determine its activity. Yamada *et al* further teach that depending on how these polynucleotide's secondary/tertiary structure are fold, activity may be gained or lost (See page 5593, column 2, second full paragraph, in particular). Segal *et al* teach that immunostimulatory sequence has the potential of inducing autoimmune disease in susceptible individual (See abstract, Figure 3, in particular).

For these reasons, it would require undue experimentation even for one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

13. Claims 1-3, 7-8, 50-51, 60-61, 63, 71-72, 74-75, 78, 83-84, 86, and 90-107 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of *any* antigen, *any* allergen, *any* pollen allergen, *any* ragweed allergen, and *any* "polynucleotide" comprising *any* immunostimulatory sequence (ISS) wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length in the population of conjugate molecules as set forth in claims 1-3, 7-8, 50-51, 60-61, 63, 71-72, 74-75, 78, 83-84, 86, and 90-107 for treating *any* condition.

The specification discloses only eight specific immunostimulatory sequences (ISS) such as SEQ ID NO: 1-8 conjugated to ragweed allergen Amb a1 (See page 72). The conjugate was prepared by incubation of a mixture of ISS at various molar concentrations such as 4, 7 or 17 molar to 1 molar concentration of Amb a1. The antibody response and histamine release from various conjugates such as AIC-L (4:1), AIC-M (7:1) and AIC-H (17-1) are measured. The AIC-H (17-1) conjugate shift the Th2 to Th1 immune response as determined by IFNγ, IL-5 levels and histamine release (page 80-82). The specification discloses the term "antigen" means any substance such as peptides, proteins, glycoproteins, polysaccharides, complex carbohydrates, sugars, gangliosides lipids, and phospholipids; portions thereof and combination thereof (page 16, liens 20-22). The specification discloses that the term "allergen" means antigen, or antigenic portion thereof of any molecule, usually a protein (see 18, lines 12-14).

With the exception of the specific population of conjugate comprising the specific immunostimulatory sequence (ISS) and the specific allergen, there is insufficient written description about the structure associated with function of any population of conjugate molecules or composition mentioned above because the term "antigen", "allergen", "pollen allergen" and "polypeptide" without the specific amino acid sequence and SEQ ID NO: have no structure, let alone having the same functions as ragweed allergen Amb a1. As to polynucleotide comprising an immunostimulatory sequence (ISS) wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length, the specification discloses only the specific ISS sequence such as SEQ ID NO: 1-8 which are no more than 22 nucleotides in length. There is inadequate written description about the nucleotides of any ISS that is "less than about 200 nucleotide in length", much less the undisclosed has immunostimulatory activity. Since the antigen and polynucleotide are not adequately described, it follows that any conjugate molecule comprising said undisclosed antigen and said undisclosed ISS are not adequately described. It also follows that any composition comprising said undisclosed population of conjugate are not adequately described.

As to claims 50, 51, 60, 61, 71, 72, 83, and 84, the term "comprising" is open-ended. It expands the ISS in the conjugate to include additional nucleotides at either or both ends of the undisclosed ISS so long the ISS is greater than 6 and less than about 200 nucleotide in length. Even if the ISS is limited to the specific polynucleotide sequence, there is insufficient written description about which undisclosed nucleotides are to be added to either or both ends of any ISS. Further, the specification discloses only one pollen allergen Amb 1 conjugated to one ISS (SEQ ID NO: 1). Given the lack of a written description of *any* additional representative species of

allergen, polypeptide, antigen, pollen allergen and ISS wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length as encompassed by the claims for a population of conjugate, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 4/14/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the pending claims are full described in the specification as filed. (2) the burden is on the Examiner to present evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims.

In response, the claims still drawn to any population of conjugate molecule comprising any antigen, and any polynucleotide comprising any immunostimulatory sequence (ISS) wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length. The specification does not reasonably provide a **written description** of *any* antigen, *any* allergen, *any* pollen allergen, *any* ragweed allergen, and *any* "polynucleotide" comprising *any* immunostimulatory sequence (ISS) wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length in the population of conjugate molecules as set forth in claims 1-3, 7-8, 50-51, 60-61, 63, 71-72, 74-75, 78, 83-84, 86, and 90-107 for treating *any* condition because of the following reasons. The term "antigen", "allergen", "pollen allergen" and "polypeptide" without the specific amino acid sequence and SEQ ID NO: have no structure, much less about its function. As to polynucleotide comprising an immunostimulatory sequence (ISS) wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length, the specification discloses only the specific ISS sequence such as SEQ ID NO: 1-8 which are no more than 22 nucleotides in length. There is inadequate written description about the nucleotides of any ISS that is "less than about 200 nucleotide in length", much less the undisclosed ISS that has immunostimulatory activity. Since the antigen and polynucleotide are not adequately described, it follows that any conjugate molecule comprising said undisclosed antigen and said undisclosed ISS are not adequately described. It also follows that any composition comprising

said undisclosed population of conjugate are not adequately described. As to claims 50, 51, 60, 61, 71, 72, 83, and 84, the term "comprising" is open-ended. It expands the ISS in the conjugate to include additional nucleotides at either or both ends of the undisclosed ISS so long the ISS is greater than 6 and less than about 200 nucleotide in length. Even if the ISS is limited to the specific polynucleotide sequence, there is insufficient written description about which undisclosed nucleotides are to be added to either or both ends of the disclosed ISS because the term comprising is open-ended. Further, the specification discloses only one pollen allergen Amb 1 conjugated to one ISS (SEQ ID NO: 1). Given the lack of a written description of *any* additional representative species of conjugate molecule, allergen, polypeptide, antigen, pollen allergen and ISS and wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length as encompassed by the claims, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

14. Claims 75, 83-84 and 86 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "**average** ratio of (i) average mass of ISS-containing polynucleotide to (ii) average mass of antigen is **at least 1.1**" in Claim 75 represents a departure from the specification and the claims as originally filed. The specification as filed does not provide a clear support for the said phrase.

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

16. Claims 1, 7, 50-51, 60-61, 71-72, 83-84, and 90-93 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "G-3'"" in claims 50 has no antecedent basis in base claim 45 because the word "G", which is a purine at the 3'end is not recited in claim 45. Claim 45 requires a pyrimidine at the 3' end. Further, claim 50 depends on non-elected claim 45. Claim 50 should depend from claim 1.

The recitation of "G-3'"" in claims 60 has no antecedent basis in base claim 55 because the word "G", which is a purine at the 3'end is not recited in claim 55. Claim 55 requires a pyrimidine at the 3' end. Further, claim 60 depends on non-elected claim 55. Claim 60 should depend from claim 2.

The recitation of "G-3'"" in claims 71 has no antecedent basis in base claim 66 because the word "G", which is a purine at the 3'end is not recited in claim 66. Claim 66 requires a pyrimidine at the 3' end. Further, claim 71 depends on non-elected claim 66. Claim 71 should depend from claim 63.

The recitation of "G-3'"" in claims 83 has no antecedent basis in base claim 78 because the word "G", which is a purine at the 3'end is not recited in claim 78. Claim 78 requires a pyrimidine at the 3' end. Further, claim 83 depends on non-elected claim 78. Claim 83 should depend from claim 75.

The "ratio of (i) concentration of ISS-antigen conjugate ... to (ii) concentration of antigen required antigen is about 3.5 to about 6.0" in claim 1 is indefinite and one of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention because the specification on page 71 discloses the number of oligonucleotide (ISS) conjugated to the number of Amb a1 which distinguishes by class. AIC-L contains an average of 2-3 oligonucleotides per Amb a 1 molecule, AIC-M contains an average of 3.5 to 4.5 and AIC-H contains an average of greater than 5.5. The specification does not disclose ISS-antigen conjugate to antigen.

Applicants' arguments filed 4/14/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the sequence recited in claim 50 includes the sequence recited in claim 45 plus two additional bases at the 3' end, C and G. (2) The rejection of claims 60, 71, and 83 should have different dependency based on the same reasoning for that of claims 50 and 45.

However, none of the dependent claimed 50, 60, 71, and 83 recite "plus two additional bases at the 3' end, C and G". All dependent claims should be narrower in scope. The "G" is a purine and not a pyrimidine. Claim 45, for example, requires a pyrimidine at the 3' end. The rejection of claims 60, 71, and 83 should have different dependency based on the same reasoning for that of claims 50 and 45. It is suggested that claim 50 be recite "the population of claim 45 wherein said immunostimulatory sequence is further consisting of CG at the 3' end", for example.

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1-3, 7-8, 50-51, 60-61, 63, 71-72, 75, 83-84, 86, and 90-107 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/16247 publication (April 1998, PTO 1449).

The WO 98/16247 publication teaches a composition of conjugate molecule wherein the reference conjugate molecule comprises an antigen (IMM) such as β-gal (polypeptide) or a pollen ragweed allergen such as Amb a I (page 19, lines 15-22, in particular) conjugated to a polynucleotide comprising an immunostimulatory sequence (ISS-PN or ISS-ODN) such as 5'TGACTGTG**AACGTTCG**AGATGA-3' (DY1018) that is a 22 mer polynucleotide identical to SEQ ID NO: 1 as disclosed on page 23 line 10 of instant specification. The WO 98/16247 publication teaches that the ISS sequence is preferably between 6 and 200 bases in length (See page 36, line 10, page 15, line 8, in particular). The reference composition further comprises a pharmaceutically acceptable excipient for modulating an immune response (See claims of the WO 98/16247, page 24, lines 9-27 bridging page 25, lines 1-9, in particular). The term "about" includes the reference ISS polynucleotide sequence of between 6 and 200 bases in length. Further, the term "comprising" is open-ended. It expands the claimed ISS to include additional nucleotides at either or both ends to include the reference immunostimulatory sequence. The reference immunostimulatory sequence 5' **AACGTTCG 3'** where nucleotides A and G are purine and nucleotide C and G are pyrimidine. The WO 98/16247 publication teaches various methods of linking the ISS to the antigen, which are known in the art (See pages 24-26, in particular). The WO 98/16247 publication further teaches that the concentration of the conjugate to the antigen is 5: 1, which is at least 1.1 (See page 7, in particular). With regard to 50%

inhibition of binding of antigen-specific antibody to antigen, it is an inherent property of the reference-conjugated antigen since the process of conjugation alters the structure of said antigen. The WO 98/16247 publication further teaches that the reference conjugate molecule such as ISS-PN, ISS-PN/IMM can shift the host cellular immune response away from the helper T lymphocyte type 2 (Th2) phenotype toward a helper T lymphocyte type 1 (Th1) phenotype and using this method to boost the immune responsiveness of a host to subsequence challenge by a sensitizing antigen without immunization can avoid the risk of Th2-mediated, immunization-induced anaphylaxis by suppressing IgE production in response to the antigen challenge. Furthermore, the reference conjugate molecule is especially advantageous for treatment of localized allergic response (See page 3, lines 8-23, in particular). The WO 98/16247 publication teaches allergen such as Amb a1 of ragweed pollen allergen can be conjugate to the polynucleotide comprising the immunostimulatory sequence (ISS-PN or ISS-ODN) (See page 19, lines 15-22, page 21-26, in particular). Given that the reference conjugate molecule has the same structure as the claimed conjugate molecule having the same extend of conjugation, the reference conjugate molecule inherently has the same function such as the population provides a 40% histamine release ratio of greater than about 500. Since the Patent Office does not have the facilities for examining and comparing the conjugate molecule of the instant invention to those of the prior art, the burden is on applicant to show that the prior art conjugate molecule is different from the claimed conjugate molecule. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Claim 63 is included in this rejection because the term the "population provides an average of at least 5.5 ISS containing polynucleotides per antigen molecule would include the reference 5 ISS containing polynucleotides per one antigen molecule. Further, the disparity in the ISS to antigen ratio may related to the different techniques used to quantify the two components of the conjugate, ie. Amino acid analysis for peptides and spectrophotometric absorbance of ISS. Claim 75 is included in this rejection because the terms average ratio of average of mass of ISS containing polynucleotide to average mass of antigen is "at least" 1.1 would include the reference number of oligonucleotides bound to Amb is 5: 1. The "mass" of the reference ISS and the mass of the reference antigen is an inherently property of the reference ISS and antigen. Since the mass ratio of ISS to antigen depends the on number of molar excess of antigen reacts with the ISS, the reference teaches that mass ratio of ISS to antigen is 5:1 which would include at least 1.1. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 4/14/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the figure legends of Carson et al state that the ISS/antigen conjugate employed are at a 5:1 (ISS:antigen) ratio. (2) Carson does not teach the claimed invention because Carson does not describe the ISS-antigen were conjugated such that the ratio of conjugate to antigen required for 50% inhibition of antigen-specific antibody to antigen binding is about 3.5 to about 6.0. (3) Carson does not describe the ISS-antigen were conjugated such that the extent of antigen and polynucleotide conjugation provides a 40% histamine release ratio of greater than about 500. (4) Carson does not describe the ISS-antigen were conjugated such that the extend of antigen and polynucleotide conjugation provides an average of at least 505 of the polynucleotides per antigen molecule or an average ratio of average polynucleotide mass to average antigen mass of at least 1.1. (5) Claim 63 is directed to a population of conjugate molecules wherein the extent of conjugation provides an *average* of at least *5.5* ISS-containing polynucleotides per antigen molecule. (6) the Office Action has not provide fact or sound technical reasoning to support the statements regarding the inherency in view of Carson. (7) The claimed invention falls into the "H" class of conjugate molecule. Nothing in Carson or in the Office Action supports that allegedly inherent characteristics of the claimed populations of conjugate molecules necessarily flows from Carson. (7) Carson teaches conjugate molecules made with 5:1 ISS antigen not conjugate to antigen. (8) The average mass ratio of claim 75 is different that the molecule ratio described by Carson. Carson does not describe conjugation to an extent that provides an average mass ratio of at least 1.1.

However, the WO 98/16247 publication teaches a composition of conjugate molecule wherein the reference conjugate molecule comprises an antigen (IMM) such as β-gal (polypeptide) or a pollen ragweed allergen such as Amb a I (page 19, lines 15-22, in particular) conjugated to a polynucleotide comprising an immunostimulatory sequence (ISS-PN or ISS-ODN) such as 5'TGACTGTG**AACGTTCG**AGATGA-3' (DY1018) that is 22 nucleotide in length and preferably between 6 and 200 bases in length (See page 36, line 10, page 15, line 8, in particular) and a pharmaceutically acceptable excipient for modulating an immune response (See claims of the WO 98/16247, page 24, lines 9-27 bridging page 25, lines 1-9, in particular). The term "about" includes the reference ISS polynucleotide sequence of between 6 and 200 bases in length. Further, the term "comprising" is open-ended. It expands the claimed ISS to include additional nucleotides at either or both ends to include the reference immunostimulatory

sequence. The reference conjugate molecule appears to have the same structure as that of the claimed population conjugate, i.e. antigen is an allergen such as Amb a1 and the ISS polynucleotide sequence is greater than 6 and less than about 200 nucleotides in length. Further, the WO 98/16247 publication teaches that the concentration of the oligonucleotide (ISS) to the antigen is 5: 1, which is within the claimed limitation of about 3.5 to about 6.0. Note that the instant specification discloses on page 71 discloses the number of oligonucleotide (ISS) conjugated to the number of Amb a1 which distinguishes by class. AIC-L contains an average of 2-3 oligonucleotides per Amb a 1 molecule, AIC-M contains an average of 3.5 to 4.5 and AIC-H contains an average of greater than 5.5. The specification does not disclose ISS-antigen conjugate to antigen per se as recited in claim 1. Since the Patent Office does not have the facilities for examining and comparing the conjugate molecule of the instant invention to those of the prior art, the burden is on applicant to show that the prior art conjugate molecule is different from the claimed conjugate molecule. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Given that the reference conjugate molecule has the same structure as the claimed conjugate molecule in the claimed population having the same extend of conjugation, the reference conjugate molecule inherently has the same function such as the population provides a 40% histamine release ratio of greater than about 500. Claim 63 is included in this rejection because the term the "population provides an average of at least 5.5 ISS containing polynucleotides per antigen molecule" would include the reference 5: 1 ISS containing polynucleotides per antigen molecule. Further, the disparity in the ISS to antigen ratio may related to the different techniques used to quantify the two components of the conjugate, ie. Amino acid analysis for peptides and spectrophotometric absorbance of ISS. Claim 75 is included in this rejection because the terms average ratio of average of mass of ISS containing polynucleotide to average mass of antigen is "at least" 1.1 would include the reference number of oligonucleotides bound to Amb is 5: 1. The "mass" of the reference ISS and the mass of the reference antigen is an inherently property of the reference ISS and antigen. Since the mass ratio of ISS to antigen depends the on number of molar excess of antigen reacts with the ISS, the reference teaches that mass ratio of ISS to antigen is 5:1 which would include at least 1.1.

In response to applicant's argument that Carson et al fails to teach anything with respect to any desirability or effect of the extents of conjugation and contains no disclosure regarding variation of the ratio or reaction time, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for

patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

21. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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